A Novel Multiscale Model of Cardiac Hypertrophy Incorporating Intracellular Signaling

Biomedical Engineering
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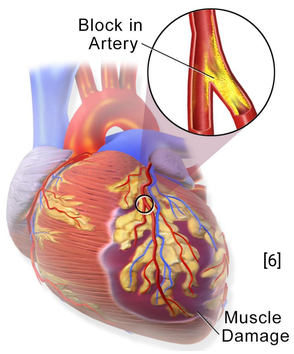
Background

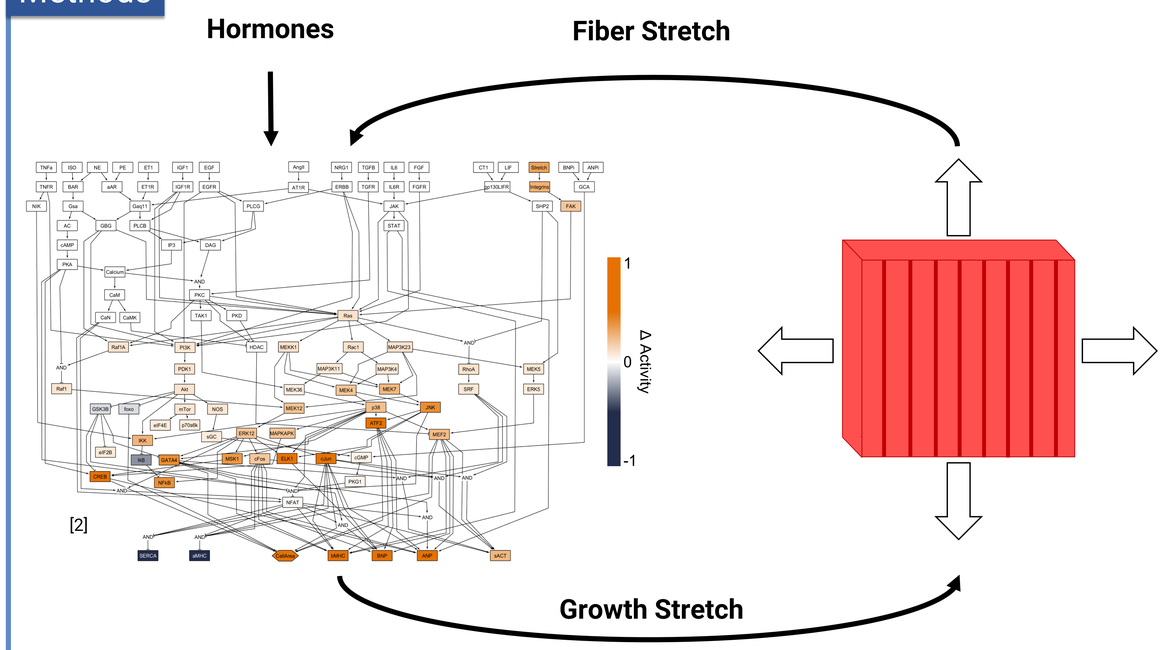
- Over 1 million Americans suffer a myocardial infarction (MI) every year[1].
- Following infarction, changes in mechanics interact with hormonal signaling to determine post-infarction growth and remodeling, dilation, and progression to heart failure, but prior growth models have focused primarily on the mechanical signals.



[6]

We present a multiscale growth model that incorporates both tissue-level mechanics and intracellular hypertrophic signaling pathways[2], and compare its behavior to published phenomenologic growth laws.

Methods



Schematic of our Multiscale Model: The published hypertrophy network model takes stretch and hormone levels as inputs and calculates cell area and gene expression as outputs. The cell area is used to calculate the amount of growth experienced by the mechanical model of the slab, which in turn determines the stretch input for the network model.

Mapping Functions

$$\boldsymbol{F}_{total} = \boldsymbol{F}_{elastic}\boldsymbol{F}_{growth}$$

$$J_{growth} = \det(\boldsymbol{F}_{growth})$$

$$\boldsymbol{\sigma} = f(\boldsymbol{F}_{elastic})$$

[5]

Stretch

$$Stretch\ Input = m \times F_{elastic,ff} + b$$

Growth

$$J_{growth} = (Cell\ Area_{new} - 0.5) \times J_{original} + J_{original}$$

$$F_{growth,ff} = F_{growth,cc} = F_{growth,rr} = J_{growth}^{\frac{1}{3}}$$

Phenomenologic Laws

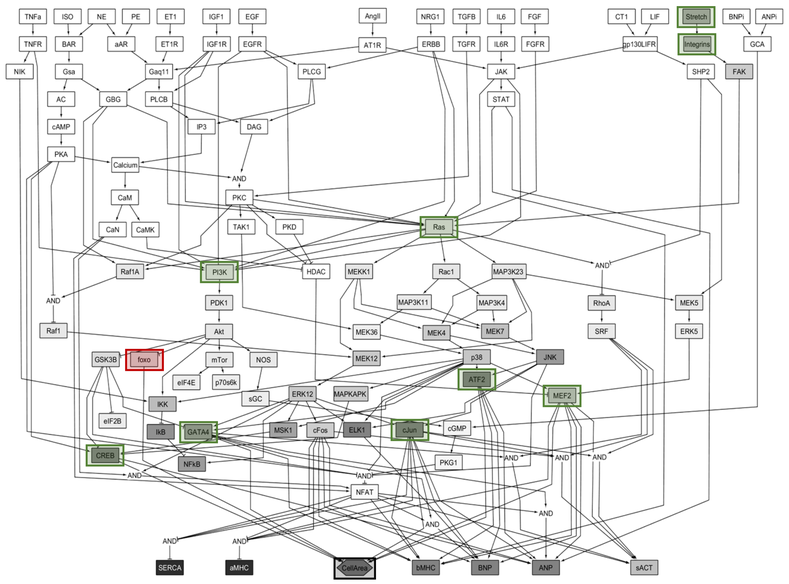
Strain Based

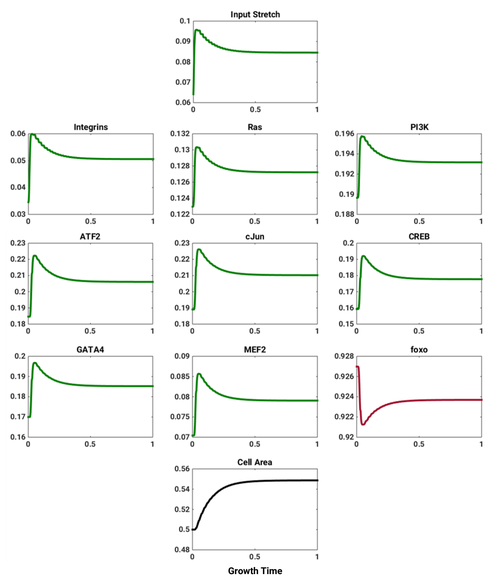
$$\frac{d\boldsymbol{F}_{growth}}{dt} = f(\Delta\boldsymbol{E}_{elastic})$$ [3]

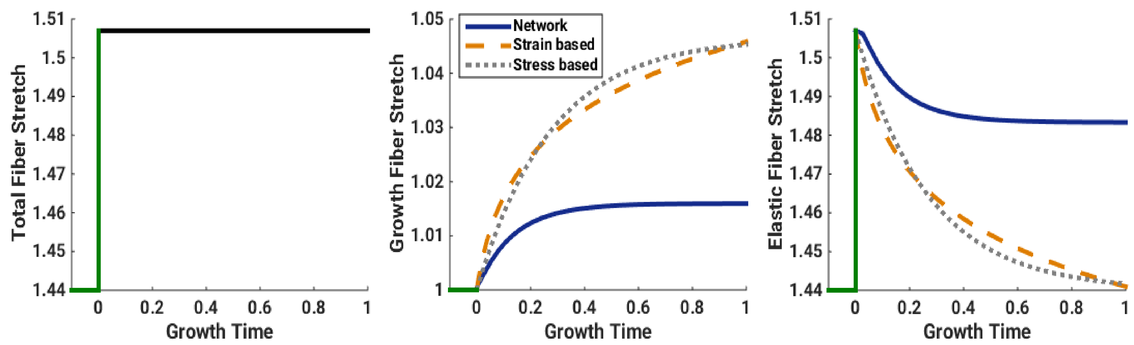
Stress Based

$$\frac{d\boldsymbol{F}_{growth}}{dt} = f(\Delta\boldsymbol{\sigma})$$ [4]

Results







Growth Predictions: Prescribed total stretch, predicted growth stretch, and computed elastic stretch following equibiaxial extension of a slab of myocardium. The two phenomenologic laws drive growth until the elastic stretch returns to the starting homeostatic value. In contrast, the multiscale model reaches a growth steady state more rapidly than the phenomenologic laws without restoring the elastic stretch back to the starting homeostatic value.

Signaling Network Model Behavior: Network diagram shows nodes that are upregulated (green) or downregulated (red) by stretch. Individual plots show time course of activation of individual network nodes.

Discussion

- The phenomenologic and signaling network models compared in this study predicted fundamentally different responses to a step increase in stretch. By design, in the phenomenologic models, stretch drove growth until elastic stretch returned to a target homeostatic value.
- In the signaling model, stretch led to an increased rate of gene expression and protein production; because protein degradation in the model was assumed to be first-order, the system achieved a new steady-state predicted cell size despite a persistently elevated elastic stretch.
- One way to reconcile these predictions might be to include mechanical regulation of protein degradation in the network model. This work represents a step towards constructing a growth model that can predict the effects of drugs such as beta-blockers that modulate cardiac remodeling.

Future Work

- Coupling the network model to a finite-element model of the left ventricle of the heart and the circulation.
- Simulating hormonal perturbations in addition to an altered mechanical state to predict growth.
- Simulating the effect of drug therapies post-injury, such as beta-blocker administration following myocardial infarction.

References and Acknowledgements

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